Synthesis and Characterization of Pyrrolo[2,3-*f*] Indole-3,7-Dicarbonitriles

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Abstract

2,6-Diamino-4,8-dioxo-1,4,5,8-tetrahydropyrrolo[2,3-f]indole-3,7-dicarbonitrile derivatives (5a-g) were prepared by treatment of chloranil with two equivalents of malononitrile in presence of a basic catalyst given dimalononitrile derivative 3, and the latter reacts with two equivalents of a series of primary aromatic or aliphatic amines bearing different substituents in the para position. The resulting compounds were characterized by elemental and spectral analyses. In addition, the biological screening of selected samples was tested.

Keywords

Quinone; Pyrrolo[2,3-f]indole; Synthesis; Characterization; Antifungal; Antibacterial

Introduction

The quinone moiety is involved in a wide variety of biochemical processes including electron transport and oxidative phosphorylation (Pratt et al., 1960). Various biological properties including enzyme inhibition, antibacterial, antifungal, and anticancer activities have been reported in quinones and quinone derivatives (David et al., 2012; Gaston et al., 2012; Tatjana et al., 2010; Vishnu et al., 2010; Hyun-Jung et al., 2007; Ryu et al., 2000; Ryu & Song et al., 2003; Wellington et al., 2012). Heterocyclic quinones, containing nitrogen atom, are known to possess antibacterial (Tandon et al., 2005; Vishnu & Dharmendra et al., 2006; Hung et al., 2004), antifungal (Ryu & Choi et al., 2003; Ryu et al., 2005; Ryu et al., 2002), and cytotoxic activities (Kuo et al., 1996; Lee et al., 2004; Gomez-Monterrey et al., 2003; Gomez-Monterrey et al., 2001). The diverse biological effects caused by incorporation of nitrogen or sulfur atoms in five- or six-membered heterocyclic ring retaining the 'core' chromophore have been one of the mainstay of structural and chemical modifications of this class of compounds (Vishnu & Hardesh et al., 2006; Gomez-Monterrey et al., 2005; Seradj et al., 2004; Brun et al., 2005; Kim et al., 2003; Dossantos et al., 2004; Tandon et al., 2004; Ryu& Shim et al., 2005; Ryu& Choi et al., 2005; Tadeusz et al., 2003; Ryu et al., 2009). In the course of a medicinal chemistry program this work aimed to the synthesis of new quinone derivatives having N atom in a five-membered ring as part of heterocyclic quinone. The presented paper describes the synthesis of a series from 2,6-diamino-1,5-di(aryl or alkyl)-4,8-dioxo-1,4,5,8-tetrahydropyrrolo[2,3-f]indole-3,7-dicarbonitrile derivatives, with good antibacterial and antifungal activities.

Experimental Part

Materials

All compounds are new details of the synthesis and characterization of these compounds is given in the experimental part. Chloranil (Sigma Aldrich, ≥99.0% %), malononitrile (Sigma Aldrich, ≥99.0%), aniline (Sigma Aldrich, ≥99.5%), *p*-hydroxyaniline (Acros, 97%), *p*-amino benzoic acid (Sigma Aldrich, ≥99.0%), *p*-chloroaniline (Acros, 98%), *p*-anisidine (Acros, 99%), *p*-toluidine (Acros, 99%), *p*-nitroaniline (Acros, 99%), ethylamine (El-Nasr Chemical Company, Egypt) and methylamine (El-Nasr Chemical Company, Egypt). Other reagents and solvents were purchased and used as received unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) using TLC silica gel coated aluminum plates 60F $_{254}$ (Merck).

Instrumentation

Elemental analyses were carried out using an Elemental Analyses system GmbH, VARIOEL, V2.3 July 1998 CHNS Mode. Infrared spectrophotometer IR spectra were recorded on IR-470, Infrared spectrophotometer, Shimadzu by using the KBr pellet technique at Assiut university, Egypt. ^{1}H NMR spectra were recorded on a varian EM-390-NMR (90 MHz) spectrometer or GNM-LA (400 MHz) spectrophotometer at room temperature in DMSO, pyridine or TFA), and chemical shifts were reported as δ values (ppm) relative to internal Me_4Si. Mass spectra were carried out by the MS route JMS-JEOL-Japan-600 H at Assiut university, Egypt.

***2-(2,5-Dichloro-4-dicyanomethyl-3,6-dioxo-cyclohexa-1,4-dienyl)-malononitrile* (3)**

A mixture of chloranil **(1)** (2.46 g, 10 mmol) and malononitrile **(2)** (0.66 g, 20 mmol) in 50 mL absolute ethanol containing few drops of triethylamine was refluxed for 30 min. Whereby the reaction colour changed gradually from yellow to green, the reaction mixture was then concentrated to about 1/3 of its volume and cooled overnight, where a precipitated crystalline green product was filtered, washed with excess water and air dried. Purification by recrystallization from dioxane gave dark green platelets; yield 93%; m.p.: 241 °C. $C_{12}H_2Cl_2N_4O_2$: Calcd. C, 47.24; H, 0.66; Cl, 23.24; N, 18.36; found: C, 47.71; H, 0.35; Cl, 23.57; N, 18.93. IR (KBr, cm^{-1}): 2243 (C≡N), 1682 (C=O of quinone) and 707 (C-Cl).

General Procedure A for preparing 2,6-diamino-1,5-di(aryl or alkyl)-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo[2,3-f]indole-3,7-dicarbonitrile (5a-j)

A mixture of compound **3** (3.05 g, 0.01 mole) in about 50 ml absolute ethanol with two equivalents of primary amines **4a-j** (0.02 mole) in about 50 ml absolute ethanol for varying periods (3-8 hours), gave stable deep red to brown colours depending on the type of the used aryl amine. A solid product precipitated at reflux, which was then stopped and the products were collected by filtration, air dried and recrystallized from the appropriate solvent. Their identification as 2,6-diamino-1,5-di(aryl or alkyl)-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo[2,3-*f*]indole-3,7-dicarbonitriles **(5a-j)** was based on both elemental and spectral data; and the amines used in this reaction were: aniline, *p*-hydroxyaniline, *p*-aminobenzoic acid, *p*-chloroaniline, *p*-anisidine, *p*-toluidine, *p*-nitroaniline, ethylamine, methylamine and ammonia **(4a-j)**.

2,6-Diamino-4,8-dioxo-1,5-diphenyl-1,4,5,8-tetrahydro-pyrrolo[2,3-f]indole -3,7-dicarbonitrile (5a)

According to the general procedure A: compound **3** (3.05 g, 10 mmol) and aniline **(4a)** (1.86 g, 20 mmol), absolute ethanol (50 mL), was heated to 82°C for 8 h. Purification by recrystallization from dioxane gave yellowish-orange crystals; yield: 65 %; m.p.: 291°C.

Anal. Calcd. for $C_{24}H_{14}N_6O_2$: C, 68.89; H, 3.37; N, 20.09. Found: C, 68.58; H, 3.41; N, 20.47. IR (KBr, cm^{-1}): 3232 & 3200 (NH str. vib.); 747 & 706 (5 adj Ar-H).

2,6-Diamino-1,5-bis-(4-hydroxy-phenyl)-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo[2,3-f]indole-3,7-dicarbonitrile (5b)

According to the general procedure A: compound **3** (3.05 g, 10 mmol) and *p*-hydroxyaniline **(4b)** (2.18 g, 20 mmol), absolute ethanol (50 mL), was heated to 82°C for 7 h. Purification by recrystallization from DMF/ benzene gave greenish-brown crystals; yield: 81 %; m.p.: >350 °C.

Anal. Calcd. for $C_{24}H_{14}N_6O_4$: C, 64.00; H, 3.13; N, 18.66. Found: C, 64.36; H, 3.60; N, 18.29. IR (KBr, cm^{-1}): 3496 (O-H str. vib.); 3247 & 3210 (NH str. vib.); 823 (2 adj Ar-H).

2,6-Diamino-1,5-bis-(4-carboxy-phenyl)-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo[2,3-f]indole-3,7-dicarbonitrile (5c)

According to the general procedure A: compound **3** (3.05 g, 10 mmol) and *p*-amino benzoic acid **(4c)** (2.74 g, 20 mmol), absolute ethanol (50 mL), was heated to 82°C for 8 h. Purification by recrystallization from DMF/H_2O gave yellowish-brown crystals; yield: 86 %; m.p.: >350 °C.

Anal. Calcd. for $C_{26}H_{14}N_6O_6$: C, 61.66; H, 2.79; N, 16.59. Found: C, 61.35; H, 2.41; N, 16.93. IR (KBr, cm^{-1}): 3263 & 3240 (NH str. vib.); 1689 (C=O of COOH) and 836 (2 adj Ar-H).

2,6-Diamino-1,5-bis-(4-chloro-phenyl)-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo [2,3-f]indole-3,7-dicarbonitrile (5d)

According to the general procedure A: compound **3** (3.05 g, 10 mmol) and *p*-chloroaniline **(4d)** (2.55 g, 20 mmol), absolute ethanol (50 mL), was heated to 82°C for

8 h. Purification by recrystallization from dioxane gave brownish red crystals; yield: 83 %; m.p.: 343 °C.

Anal. Calcd. for $C_{24}H_{12}Cl_2N_6O_2$: C, 59.15; H, 2.48; Cl, 14.55 ; N, 17.25. Found: C, 59.45; H, 2.17; Cl, 14.92; N, 17.39. IR (KBr, cm^{-1}): 3232 & 3210 (NH str. vib.); 831 (2 adj Ar-H); 771 (C-Cl).

2,6-Diamino-1,5-bis-(4-methoxy-phenyl)-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo[2,3-f]indole-3,7-dicarbonitrile (5e)

According to the general procedure A: compound **3** (3.05 g, 10 mmol) and *p*-anisidine **(4e)** (2.46 g, 20 mmol), absolute ethanol (50 mL), was heated to 82°C for 6 h. Purification by recrystallization from dioxane gave reddish-brown crystals; yield: 57 %; m.p.: >350°C.

Anal. Calcd. for $C_{26}H_{18}N_6O_4$: C, 65.27; H, 3.79; Cl, 14.55 ; N, 17.56. Found: C, 65.02; H, 3.35; N, 17.90. ^{1}H NMR (pyridine): δ =3.68 (s, 6H, $2CH_3$), 5.05 (s, 4H, $2NH_2$), 7.02 (d, 4H, Ar-H) and 7.19 (d, 4H, Ar-H).

2,6-Diamino-4,8-dioxo-1,5-di-p-tolyl-1,4,5,8-tetrahydro-pyrrolo[2,3-f]indole-3,7-dicarbonitrile (5f)

According to the general procedure A: compound **3** (3.05 g, 10 mmol) and *p*-toluidine **(4f)** (2.14 g, 20 mmol), absolute ethanol (50 mL), was heated to 82°C for 6 h. Purification by recrystallization from dioxane gave yellowish brown crystals; yield: 69 %; m.p.: 303 °C.

Anal. Calcd. for $C_{26}H_{18}N_6O_2$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.74; H, 4.41; N, 18.56. ^{1}H NMR (DMSO): δ =2.30 (s, 6H, $2CH_3$), 2.51 (s, 4H, $2NH_2$), 7.04 (d, 4H, Ar-H) and 7.16 (d, 4H, Ar-H).

2,6-Diamino-1,5-bis-(4-nitro-phenyl)-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo [2,3-f]indole-3,7-dicarbonitrile (5g)

According to the general procedure A: compound **3** (3.05 g, 10 mmol) and *p*-nitroaniline **(4g)** (2.76 g, 20 mmol), absolute ethanol (50 mL), was heated to 82°C for 7 h. Purification by recrystallization from dioxane gave yellowish orange crystals; yield: 81 %; m.p.: 218 °C.

Anal. Calcd. for $C_{24}H_{12}N_8O_6$: C, 56.70; H, 2.38; N, 22.04. Found: C, 56.58; H, 2.25; N, 22.35. IR (KBr, cm^{-1}): 3221 & 3200 (NH str. vib.); 1571 & 1302 (NO_2, aromatic); 833 (2 adj Ar-H).

2,6-Diamino-1,5-diethyl-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo[2,3-f]indole-3,7-dicarbonitrile (5h)

According to the general procedure A: compound **3** (3.05 g, 10 mmol) and *p*-nitroaniline **(4h)** (1.63 g, 20 mmol), absolute ethanol (50 mL), and sodium bicarbonate (2.52 g, 30 mmol) was heated to 82°C for 4 h. Purification by recrystallization from dioxane gave violet crystals; yield: 85 %; m.p.: 239 °C.

Anal. Calcd. for $C_{16}H_{14}N_6O_2$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.46; H, 4.55; N, 26.41. ^{1}H NMR (TFA): δ =3.61 (s, 6H, $2CH_3$).

2,6-Diamino-1,5-dimethyl-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo[2,3-f]indole -3,7-dicarbonitrile (5i)

According to the general procedure A: compound **3** (3.05 g, 10 mmol) and methylaminehydrochloride **(4i)** (1.35 g, 20 mmol), absolute ethanol (50 mL), and sodium bicarbonate (2.52 g, 30 mmol) was heated to 82°C for 3 h. Purification by recrystallization from dioxane gave yellowish-brown crystals; yield: 89 %; m.p.: 271 °C.

Anal. Calcd. for $C_{14}H_{10}N_6O_2$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.35; H, 3.81; N, 28.12. ^{1}H NMR (TFA): δ =1.32 (t, 6H, $2CH_3$); δ =3.89 (q, 4H, $2CH_2$).

2,6-Diamino-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo[2,3-f]indole-3,7-dicarbonitrile (5j)

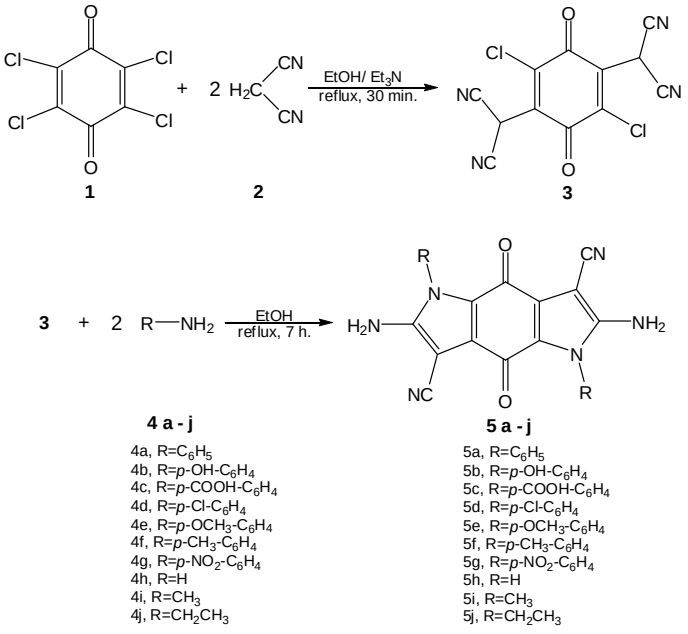
According to the general procebure A: compound **3** (3.05 g,10 mmol) and ammonia solution **(4j)** (0.70 g, 20 mmol), absolute ethanol (50 mL), and sodium bicarbonate (2.52 g, 30 mmol) was heated to 82°C for 3 h. Purification by recrystallization from dioxane gave yellowish-brown crystals; yield: 78 %; m.p.: >350 °C.

Anal. Calcd. for $C_{14}H_6N_6O_2$: C, 54.14; H, 2.27; N, 31.57. Found: C, 54.65; H, 2.24; N, 31.09. IR (KBr, cm^{-1}): 3253 (NH str. vib.).

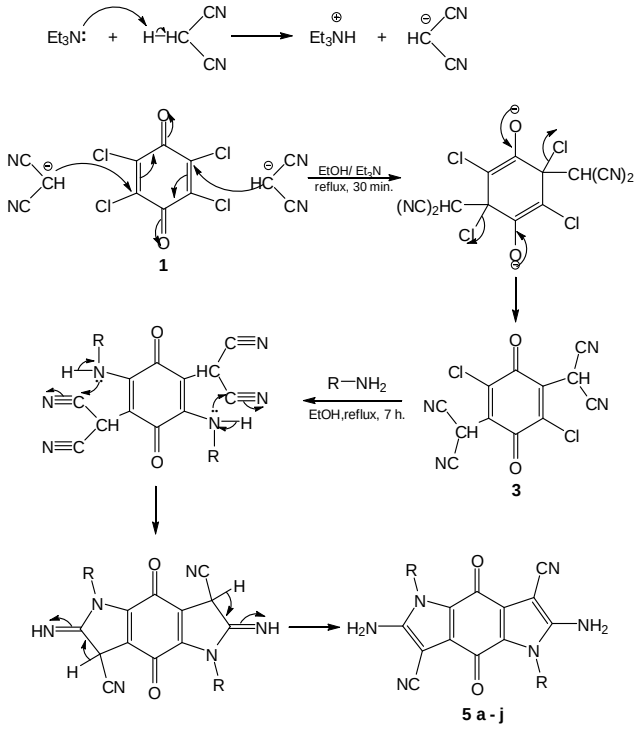
Results and Discussion

Ryu *et al* (Ryu et al., 2009) reported the synthesis of 2-amino-1-alkyl or aryl-4,9-dioxo-4,9-dihydro-1H-benzo[*f*]indole-3-carbonitriles using 2,3-dichloronaphtho-quinone. In previous report (Kim et al., 2008) on structure-activity relationships "the authors indicated that the number and position of the nitrogen atoms in the heterocyclic quinone were significant factors to affect the biological activity". Taking these

observations into consideration with an aim to prepare heterocyclic quinones containing more nitrogen atoms, we attempted the preparation of bis-heterocyclic quinones from chloranil as a starting material using Ryu's procedure (Ryu et al., 2009). Thus, treating chloranil **(1)** with two equivalents of malononitrile **(2)** in presence of a basic catalyst (triethylamine) under refluxing conditions for 30 min. to give readily the dimalononitrile derivative **3** in quantitative yield. Refluxing the latter with two equivalents of a series of primary aromatic amines bearing different substituents in the para position (a, aniline; b, *p*-hydroxyaniline; c, *p*-aminobenzoic acid; d, *p*-chloroaniline; e, *p*-anisidine; f, *p*-toluidine and g, *p*-nitroaniline) **(3a-g)** in absolute ethanol as a solvent for periods of (5-8 hours) until the reaction mixture attained stable deep red to brown colours followed by concentration and cooling of the latter solutions precipitated 2,6-diamino-1,5-diaryl-4,8-dioxo-1,4,5,8-tetrahydro-pyrrolo[2,3-*f*]indole-3,7-dicarbonitriles **(5a-g)**. Substituting the aromatic amines by aliphatic amines such as methylamine **(4h)** or ethylamine **(4i)** in the above reaction gave the 1,5-dialkyl analogues **5h** and **5i** during shorter time (3-4 hours) in quantitative yields. Liquid ammonia **(4j)** similarly reacted with the dimalononitrile derivative **3** giving the corresponding 1,5-dihydroderivative **(5j)** (SCHEME 1).



SCHEME 1: SYNTHESIS OF PYRROLO [2,3-*F*]INDOLE-3,7-DICARBONITRILES **5 A-J**



SCHEME 2 REACTION MECHANISM FOR PREPARATION OF PYRROLO [2,3-*F*]INDOLE-3,7-DICARBONITRILES **5 A-J**

The mechanism for formation of compounds **(5a-j)** is suggested to proceed as shown in SCHEME 2. All compounds were synthesized on the gram scales and obtained as analytically pure materials after recrystallization. The structures of the resulting compounds were also established from elemental analyses and spectral data, which are included in the experimental part. The IR spectral data of all quinone derivatives showed characteristic absorption band at 2250-2260 cm^{-1} for C≡N, 1660 -1682 cm^{-1} for C=O of quinones, In addition, other characteristic absorption bands due to specific groups were presented in the various derivatives.

Antimicrobial Screening

The antimicrobial screening of selected compounds **5c**, **5d**, **5f**, **5g** was performed using the standard agar diffusion method, against different organisms (fungal and bacterial species) including: Aspergillus flavus, Candida albicans, fusarium oxysporum, Geotrichum candidum, Scopulariopsis

brevicaulis, Trichophyton rubrum, Bacillus cereus (+ve), Escherichia coli (-ve), Pseudomonas aeruginosa (-ve), Staphylococcus aureus (+ve) and Serratia marcescens (-

ve). The fungal species were maintained on sabouraud dextrose agar (SDA) whereas the bacterial species were maintained on nutrient agar (NA).

Antifungal and antibacterial activities of the tested quinones were determined as described before (Pai et al., 1995), the size of the resulting inhibition zone was determined in TABLES 1,2 respectively. It can be seen from TABLE 1 that compounds **5c** and **5g** showed strong antifungal activity against the selected fungi, while **5d** and **5f** showed moderated antifungal activity against them. Meanwhile, compounds **5c** and **5g** showed strong antibacterial activity against the selected bacteria, while **5d** and **5f** showed moderated antibacterial activity against them as shown in TABLE 2.

TABLE 1 RESULTS OF ANTIFUNGAL ACTIVITY FOR COMPOUNDS **5C, 5D, 5F** AND **5G**.

Compound No. / Fungus	5c	5d	5f	5g	Control (1)
Aspergillus flavus	24	0	0	20	30
Candida albicans	17	0	8	13	27
Fusarium oxysporum	22	10	8	20	20
Geotrichum candidum	14	0	0	16	24
Scopulariopsis brevicaulis	20	0	0	18	26
Trichophyton rubrum	25	0	0	22	35

Control (1) = Clotrimazole (as antifungal standard)

TABLE 2 RESULTS OF ANTIBACTRERIAL ACTIVITY FOR COMPOUNDS **5c, 5d, 5f** and **5g**.

Compound No. / Bacteria	5c	5d	5f	5g	Control (2)
Bacillus cereus (+ve)	11	0	0	11	20
Escherichia coli (-ve)	14	0	0	11	36
Pseudomonas aeruginosa (-ve)	14	14	0	14	28
Serratia marcescens (-ve)	15	7	0	14	18
Staphylococcus aureus (+ve)	14	8	8	12	38

Control (2) = Chloramphenicol (as antibacterial standard)

FIGURES 1, 2 provide a comparative account of the effect of the selected quinone derivatives on the growth of some fungi and bacteria respectively. These results indicate that the pyrrolindole-3,7-dicarbonitiles significantly inhibit the growth of microorganisms.

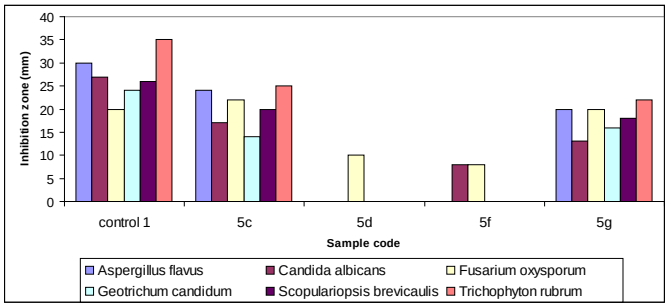


FIG. 1 EFFECT OF COMPOUNDS **5c, 5d**, **5f** AND **5g** ON THE GROWTH OF FUNGI

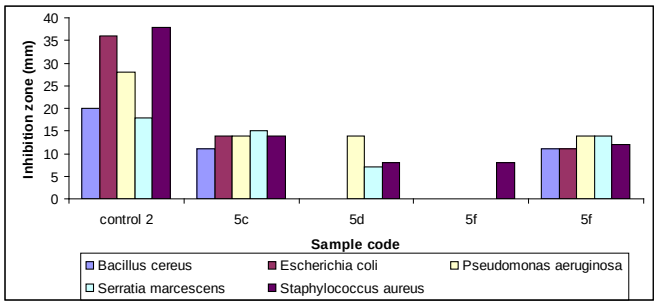


FIG. 2 EFFECT OF COMPOUNDS **5c, 5d**, **5f** AND **5g** ON THE GROWTH OF BACTERIA

It can be clarified from these figures that, the control culture generally exhibited maximum growth. On the other hand, the selected samples gave different growth which may be attributed to the different in their structures.

Conclusion

In this research study new interesting derivatives of pyrroloindole dicarbonitriles 5a-j were synthesized. The various characteristics of the resulting compounds were tested. The majority of the selected compounds were found to be highly potent against some pathogenic bacteria and fungi.

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